Th1 Lymphokine Production Profiles of Nickel-Specific CD4+ T-Lymphocyte Clones from Nickel Contact Allergic and Non-Allergic Individuals

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Panels of nickel-specific T-lymphocyte clones (TLC) were prepared from nickel-allergic and non-allergic donors. TLC from both panels showed similar levels of expression of TCRα/β, CD4, CD2, CD25, and CD29 and recognized nickel in association with class II HLA molecules with restriction determinants in HLA-DR, HLA-DP, and HLA-DQ. The lymphokine secretion was analyzed in TLC from both panels upon antigen-specific or non-specific stimulation and was compared with the secretion profiles of representants of pre-established human atopen-specific Th1 and Th2 cells. Nickel-specific TLC from both panels showed a lymphokine secretion pattern similar to the atopen-specific Th1 cells, although there was some variation from clone to clone. Most TLC secreted substantial amounts of IFN-γ, IL-2, TNF-α, and GM-CSF, but little or no IL-4 and IL-5. The variation observed mainly concerned IL-2 secretion that could be low or absent in some of the TLC. The general secretion pattern did not change upon different modes of stimulation, including activation via CD3, CD2, or CD28. Because nickel-specific TLC from allergic and non-allergic individuals show a similar Th1 secretion pattern, the present results give no evidence that aberrant lymphokine secretion by CD4+ T cells determines the contact allergic state, as was found for atopic allergy in a previous study. *J Invest Dermatol 98:59–63, 1992*

Studies in experimental animal models showed that contact dermatitis is a chronic delayed type of hypersensitivity reaction mediated by CD4+ or CD8+ T lymphocytes that are specific for the relevant allergen [1,2]. There is evidence that at least CD4+ T cells play a vital role in nickel contact dermatitis in man. Peripheral blood mononuclear cells from nickel-allergic patients show significantly higher proliferative responses to nickel when compared to non-allergic control individuals (reviewed in [3]) and it was demonstrated that the majority of these nickel-reactive cells express CD4 [4]. These data strongly suggest that peripheral blood of nickel-allergic patients harbors an elevated frequency of nickel-specific CD4+ T cells. Testing the nickel reactivity within panels of T-lymphocyte clones (TLC) randomly prepared from biopsies of experimentally nickel-induced skin lesions in nickel-allergic individuals, it was found that nickel-specific CD4+ T cells occur in relatively high frequencies in these skin lesions as well [5]. Almost all nickel-specific TLC recognized nickel in association with class II MHC molecules on the cell surface of antigen-presenting cells (APC) [6,7]. Whereas all TLC tested recognized nickel on the cell surface of Langerhans cells, only about half of these TLC could recognize nickel when it was presented by monocytes [5]. This phenomenon did not reflect entirely different populations of nickel-specific T cells, but appeared to be due to a higher level of surface sialation of cells in a lower stage of activation. One cycle of in vitro re-stimulation with a mitogen or treatment of either the monocytes or the TLC with neuraminidase could overcome the inability to proliferate to nickel presented by monocytes [8]. So far, the function of human nickel-specific CD4+ T cells was poorly studied.

Based on analysis of lymphokine production profiles, mouse CD4+ TLC can be divided in Th1 and Th2 subsets [9]. Both subsets secrete IL-3, TNF-α, and GM-CSF. Only Th1 cells secrete IFN-γ and IL-2, and only Th2 cells secrete IL-4 and IL-5. IFN-γ is considered to be a major factor in the expression of delayed type hypersensitivity (DTH) in both mouse [10] and man [11,12]. Only T cells from the IFN-γ–producing Th1 subset were able to transfer DTH [13]. Sinigaglia et al [6] reported that nickel-specific TLC from nickel-allergic donors produced IFN-γ, in combination with IL-2. The categorization of these TLC as Th1 cells, however, remains to be established. Recently, we obtained evidence for the existence of subsets of human CD4+ T cells that significantly differ in lymphokine profiles [14,15]. Atopen-specific TLC from non-atopic donors were Th1-like cells that produced IFN-γ but no substantial IL-4, whereas atopen-specific TLC from atopic patients were Th2-like cells that produced IL-4 without IFN-γ. More recent data showed that only Th2 cells secreted substantial IL-5 and that they secreted much less IL-2 [16]. The coincidence of high IL-4 and IL-5 and low IFN-γ secretion by atopen-specific Th2-like cells from atopic patients may explain some of the characteristics of atopic disease, e.g., IgE-mediated hypersensitivity and eosinophilia.

The present study was aimed to compare the lymphokine secretion patterns of nickel-specific CD4+ TLC from nickel-allergic and non-allergic individuals and to determine whether these production

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Abbreviations:
APC: antigen-presenting cells
IFN: interferon
IL: interleukin
PMA: phorbolmeristic acetate
Th: T helper
TLC: T-lymphocyte clones

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Table I. Proliferative Response to Nickel of Peripheral Blood Cells from Two Nickel-Allergic and One Non-Allergic Donor

	Nickel Patch Test	Proliferative Response (cpm $\times 10^{-3}$)	
		No Antigen	Nickel
Donor T	+	2.3 ± 0.8	23.4 ± 4.6
Donor H	+	1.8 ± 0.9	7.6 ± 2.1
Donor K	−	1.7 ± 1.1	3.3 ± 1.2

profiles fit the profiles of the pre-established functional subsets. Possibly, the secretion profiles of nickel-specific TLC from nickel-allergic patients differ essentially from those of non-allergic individuals, explaining the development of disease, analogous to atopic allergy. According to the above-mentioned data, nickel-specific TLC from nickel-allergic patients can be expected to be Th1 cells that secrete IFN-γ and IL-2, whereas the secretion pattern of the nickel-specific TLC from control individuals is difficult to predict. In the present study we have challenged this question using panels of nickel-reactive $CD4^+$ TLC from two allergic patients and a non-allergic control donor.

MATERIALS AND METHODS

Antibodies Antibodies used were WT31 (anti-TCRα/β) and B 21/7 (anti-HLA-DP) from Beckton Dickinson (Mountain View, CA); OKT4 (anti-CD4) and OKT8 (anti-CD8) from Ortho Pharmaceutical Corp. (Raritan, NJ); 2H4 (anti-CD45RA) and 4B4 (anti-CD29) from Coulter Clone (Hialeah, FL); CLB-IL2R (anti-CD25), CLB-CD27/2 (anti-CD27), CLB T3/3 (anti-CD3), CLB-T11.1/1 and CLB-T11.2/1 (both anti-CD2), and CLB-CD28/1 (anti-CD28) from Central Laboratory Blood Transfusion Service (Amsterdam, The Netherlands); B.8.11.2 (anti-HLA-DR) made available by Dr. F. Koning (Department of Immunohematology, Medical Faculty, University of Leiden); and SPV L3-8 (anti-HLA-DQ), a gift of Dr. H. Spits (DNAX, Palo Alto, CA).

Cells Peripheral venous blood was drawn from two nickel-allergic donors and one non-allergic donor. Nickel allergy was defined by a positive standardized patch test read after 48 and 72 h. PBMC were isolated from the blood by density centrifugation. Nickel-specific T-cell lines were prepared by culture of 1.5×10^5 PBMC in 96-well flat-bottom culture plates (Costar, Cambridge, MA) in 200 μl IMDM (GIBCO, Paisley, UK) supplemented with 10% complement-inactivated pooled human serum and gentamycin (80 mg/l) in the presence of 10^{-4} M $NiSO_4$. Recombinant human IL-2 (rIL-2; 20 U/ml, Cetus Corp, Emeryville, CA) growth factor was added on day 6. After 8–12 d TLC were prepared as described before [14] by re-stimulation cell-line cells in limiting dilution conditions in the presence of PHA (0.5 μg/ml PHA-P, Difco, Detroit, MI), feeder cells (irradiated allogeneic PBMC and EBV-B cells), and rIL-2 growth factor.

Assays Proliferative responses of PBMC to nickel were measured as reported earlier [7] by culturing 1.5×10^5 PBMC in 96-well flat-bottom culture plates in the presence of 10^{-4} M $NiSO_4$. In similar conditions the nickel-reactivity of TLC was assayed by culturing 2×10^4 TLC cells with 10^5 autologous 3000 rad-irradiated PMBC as a source of APC for nickel. During the last 16 h, 0.3 μCi/well tritiated thymidine (Radiochemical Centre, Amersham, UK) was present in the cultures. Proliferation in PBMC cultures was determined on day 6 and in TLC cultures on day 3 by harvesting the cells and measuring incorporation of radiolabel using a scintillation counter.

Cytokine secretion was measured in 24-h supernatants of stimulated TLC, unless stated otherwise. TLC cells, 4×10^4 (or 2×10^5), were cultured in 100 μl IMDM supplemented with 10% FCS (Flow, Irvine, UK), 35 mg/l transferrin (Behring, Marburg, FRG), 150 IU/l insulin (Novo, Copenhagen, Denmark), and 80 mg/l gentamycin and stimulated either with 10^{-4} M $NiSO_4$ in the presence of 4×10^4 (or 10^5, respectively) purified monocytes as APC, with a combination of 10 μg/ml ConA (Pharmacia, Uppsala, Sweden) and 1 ng/ml PMA (Sigma Chemical Company, Saint Louis, MO), with anti-CD3 MoAb (CLB-T3/3; immobilized by coating the culture well with 1:10,000 dilution of ascites), with a pair of anti-CD2 MoAb (CLB-T11.1/1 and CLB-T11.2/1; 1:1000 dilution of ascites), or with a combination of anti-CD28 (CLB-28/1; 1:1000 dilution of ascites) and PMA (1 ng/ml). All CLB MoAb were kind gifts of Dr. R.A.W. van Lier, Central Laboratory Blood Transfusion Service, Amsterdam, The Netherlands.

Cytokine assays were as follows: secretion of IL-4 and IFN-γ was measured using sandwich ELISA techniques as described elsewhere [17,18]. IL-2 and IL-5 activities were measured in bioassays using the murine CTLL-2 and B13 [19] cell lines, respectively. The TNF-α assay was an immunoradiometric assay and GM-CSF was determined in a solid-phase ELISA, both obtained from Medgenix Diagnostics (Soesterberg, The Netherlands). Recombinant cytokines were used as references in all assays except IFN-γ, which was referred to a natural IFN-γ standard.

Table II. Restriction Determinants of Nickel-Specific TLC from Allergic and Non-Allergic Individuals

	% Suppression with MoAb Against			HLA-II Restriction
	DR	DP	DQ	
Allergic TLC				
Fa1	98	6	14	DR
Fa2	11	48	10	DP
Fa12	0	96	3	DP
Fa22	9	0	100	DQ
Fb8	0	0	100	DQ
Fb20	0	14	100	DQ
TAB19	88	nt	32	DR
TAB31	32	nt	97	DQ
TAB38	97	nt	−11	DR
Non-allergic TLC				
MBE.D27	91	24	39	DR
MBE.D44	0	13	70	DQ
MBE.D50	100	0	15	DR
MBE.D51	99	7	31	DR
MBE.D60	0	87	15	DP
MBE.D89	96	16	3	DR
MBE.D106	0	13	70	DQ

RESULTS

Preparation and Characterization of Nickel-Reactive TLC Nickel-allergic individuals were selected for having a positive patch test read at 48 and 72 h after epicutanous nickel sulphate application. Peripheral blood T cells showed relatively high proliferative responses to nickel when compared to proliferation of the peripheral blood T cells of a non-allergic individual (Table I). Nickel-specific T-cell lines were generated by the addition of growth factor to the proliferating T cells on day 6 and TLC were prepared by re-stimulation of cell-line cells under limiting dilution conditions.

Nine nickel-reactive TLC obtained from the cell lines of the nickel-allergic donors (F and TAB series) and seven obtained from the non-allergic control (D series) were studied in more detail. Some of the properties of the nickel-reactive TLC (TAB series) from the second allergic donor have been described before [7]. The TLC all expressed comparable high levels of TCR α/β, CD4, CD25 (IL-2 receptor), HLA-DR, and CD29 and no CD27, CD45RA, and CD8 (data not shown). Proliferation to nickel only occurred when nickel was presented by autologous antigen-presenting cells (APC). Nickel-specific proliferation of the TLC was differentially blocked by antibodies to HLA-DR, HLA-DP, or HLA-DQ in both panels (Table II), indicating that nickel recognition was

Table III. Lymphokine Production by Nickel-Specific TLC upon Different Modes of Stimulation

	Nickel-Reactive TLC					
	Fa12			MBE.D50		
	IL-2 (U/ml)	IFN-γ (ng/ml)	IL-4 (ng/ml)	IL-2 (U/ml)	IFN-γ (ng/ml)	IL-4 (ng/ml)
Antigen + APC	0.9	12.3	<0.1	0.5	4.8	<0.1
Anti-CD3 MoAb	1.9	9.0	<0.1	2.1	10.6	0.1
Anti-CD2 MoAb pairs	1.2	10.4	<0.1	1.6	8.4	0.1
Anti-CD28 + PMA	2.6	15.1	0.2	2.6	12.8	0.3

restricted by MHC class II molecules and that no obvious preferential restriction determinants were present in either panel.

Lymphokine Production Profiles TLC from both panels were assayed for lymphokine secretion in response to stimulation with nickel presented by autologous monocytes or with a combination of ConA and PMA. Supernatants were harvested 24 h after onset of stimulation, which appeared in earlier experiments to be an optimal time point for cytokine secretion measurements [14]. IL-2 and IL-5 secretion was determined in proliferative bioassays; IFN-γ, IL-4, and GM-CSF secretion in ELISA; and TNF-α in a RIA. The levels of cytokine secretion by the nickel-specific TLC were compared with the levels of secretion by the atopen-specific Th1-like TLC MBE.AA42 and the atopen-specific Th2-like TLC MBB.AA60 as observed upon stimulation with ConA and PMA. No obvious differences were found between the secretion patterns of the nickel-specific TLC from allergic and non-allergic donors and stimulation with either antigen or ConA. Nickel-specific TLC from both panels produced GM-CSF and TNF-α and high levels of IFN-γ, comparable to the levels produced by atopen-specific Th1-like cells (Fig 1). Most TLC secreted IL-2, although the amount of secretion varied considerably from clone to clone. Some of the TLC secreted a little IL-4 and IL-5, but the amounts were low when compared to the atopen-specific Th2-like cells. With this secretion pattern, nickel-specific TLC both from the patients and from the control donor resembled Th1 clones, as defined previously in mouse and human.

The characteristic Th1 secretion pattern did not alter with elongation of the stimulation period up to 72 h (data not shown). Furthermore, there is no evidence for essential changes in secretion profiles using different modes of stimulation that trigger T cells via different cell-surface molecules. In representative TLC from both panels of nickel-specific TLC stimulations with either immobilized anti-CD3 antibody, a pair of anti-CD2 antibodies, or the combination of anti-CD28 antibody and PMA, all resulted in secretion of IFN-γ and IL-2 and little or no IL-4 and IL-5 (Table III).

DISCUSSION

The present study indicated that nickel-specific TLC can be prepared not only from allergic patients but also from a non-allergic donor with a nickel-induced proliferative response twice as high as the background proliferation. The nickel-specific TLC we obtained were common $CD4^+$ T cells with a TCR α/β, expressing activation markers such as CD29, CD25 (IL-2R), and HLA-DR. Nickel-specific T cells recognized nickel in association with HLA-II molecules and the restriction determinants were rather diverse. They could be found on all subclasses of HLA class II molecules, e.g., HLA-DR, HLA-DP, and HLA-DQ, supporting our previous observation [7] that the T cells involved in recognition of nickel are diverse.

Unlike the variation in restriction determinants, the nickel-specific TLC all showed a similar cytokine secretion profile, resembling Th1 cells as defined in mouse [9] and human [14]. Although they showed some individual variation, in general terms they secreted substantial to high levels of IFN-γ, IL-2, GM-CSF, and TNF-α, but hardly any IL-4 and IL-5. Some variation was observed in IL-2 production, being low or even undetectable in some cases. In fact, these TLC did secrete some IL-2, but this was only evident in concentrated cell cultures (data not shown). Although quantitative changes in secreted lymphokines were evident, no notable changes in the patterns of cytokine secretion were observed upon stimulation of the TLC via either CD3, CD2, or CD28. This observation suggests that the restrictive Th1 secretion profile does not result from selective triggering of the T cells via one of the alternative activation pathways.

Previous studies in the mouse demonstrated that responses to different antigens administered via different immunization pathways can be associated with preferential outgrowth of either antigen-specific Th1 or antigen-specific Th2 cells. Analysis of short-term antigen-specific TLC showed that repeated intraperitoneal immunizations of mice with *Brucella abortus* (Ba) protein during a 70-d period had resulted in differentiation of Ba-specific Th cells with a diffuse cytokine secretion pattern into Ba-specific Th cells with the restricted Th1 secretion pattern [20]. In contrast, infection with the parasite *Nippostrongylus brasiliensis* (Nb) resulted in selective outgrowth of Nb-specific Th2 cells. The present study suggests that responses of $CD4^+$ T cells to contact allergens, which enter the body via epidermal skin, are associated with the selective outgrowth of contact allergen-specific Th1 cells.

With respect to the possible role of $CD4^+$ T cells in contact allergy, it is noteworthy that only Th1 cells are able to transfer DTH in mice [9] and a study by Fong et al [10] gave evidence that IFN-γ, produced by this Th1 subset, plays an important role in the elicitation of DTH. In the study of Fong et al, anti-IFN-γ could inhibit footpad swelling responses induced by Th1 clones. The precise mechanism of this action of IFN-γ, however, is unclear. In vivo effects of IFN-γ in man are induration, erythema, and infiltrations of mononuclear phagocytes [11,12], whereas in rats, infiltration of lymphocytes and increase of vascular permeability were described [21,22]. In vitro, IFN-γ activates macrophages to produce higher levels of leucotriene B4, which is chemotactic for granulocytes and macrophages [23]. Fong et al were unable to block Th1-induced DTH elicitation in one of the tested mouse strains and elicitation in one model of tuberculin type DTH. Therefore, other T-cell-derived lymphokines may also play a role in the elicitation of DTH responses. Such factors may be the Th1-derived lymphokines lymphotoxin and IL-2 [24], or the Th1/Th2 cell-derived lymphokines IL-3 and GM-CSF, which have stimulating effects on macrophages [25,26]. To date it is unclear, however, whether these factors can induce inflammation by themselves or merely act as co-activators.

The observation that $CD4^+$ nickel-specific TLC both from allergic and non-allergic donors seem to be Th1 cells with very similar lymphokine secretion patterns does not support the concept that elicitation of hypersensitivity in nickel contact dermatitis is due to aberrant lymphokine production by nickel-reactive $CD4^+$ T cells of allergic patients, as was found for atopen-specific T cells in atopic dermatitis [14]. The present study was focused on $CD4^+$ T cells, because these T cells determine the magnitude of proliferative responses in vitro to nickel in cultures of peripheral blood cells [4] and because they are readily cloned from blood [6,7] and lesional skin [5]. However, the role of $CD4^+$ T cells in contact allergy is not unequivocally established. Although mouse model experiments have stressed the importance of $CD4^+$ T cells in contact allergy [1], other experiments suggested that contact allergy is predominantly

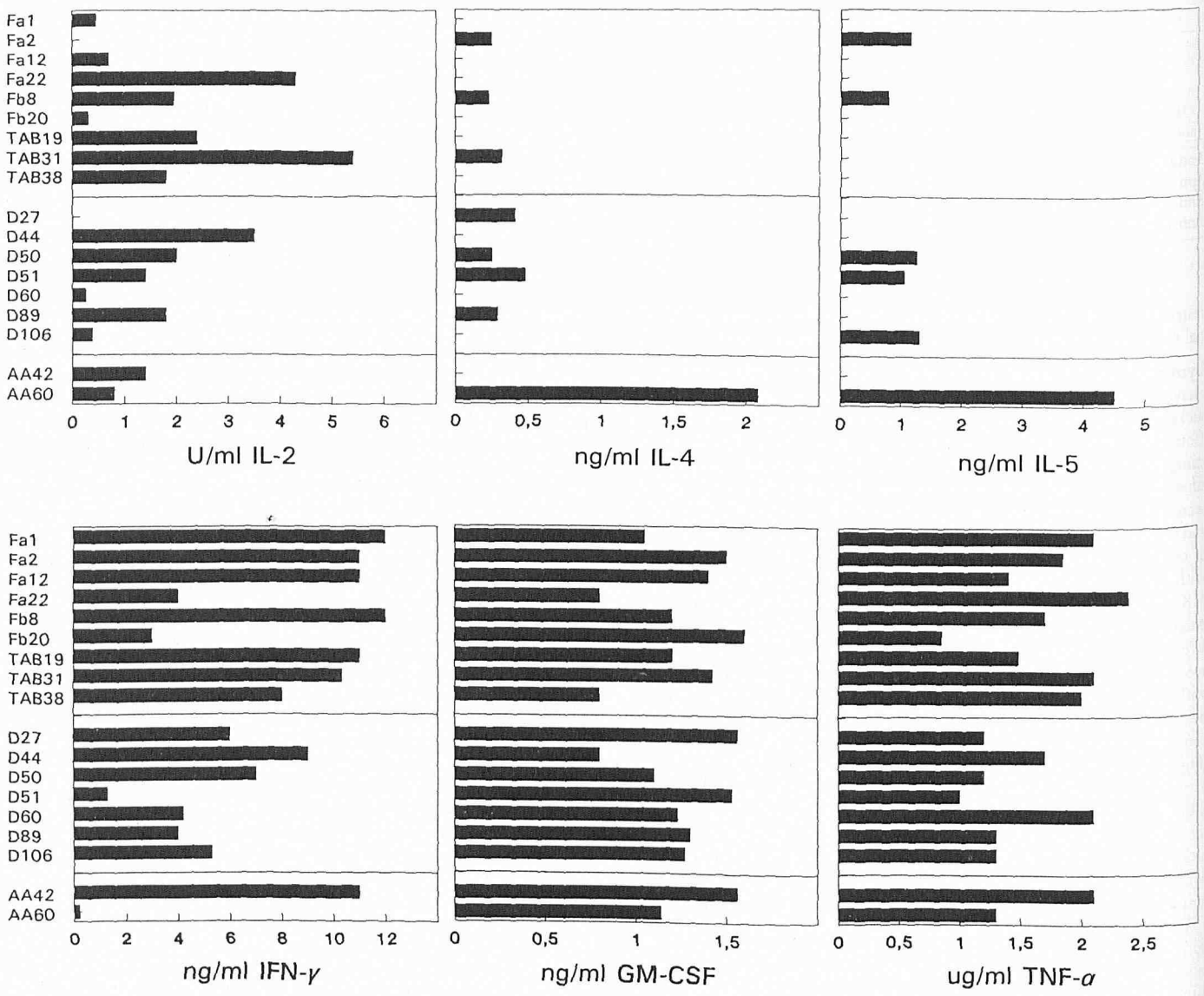

Figure 1. Cytokine production by nickel-specific TLC from panels of nickel-allergic (F and TAB series) and non-allergic (D series) donors. Cytokine production was measured in the supernatants of TLC cells ($4 \times 10^4/100\,\mu l$ culture medium) stimulated for 24 h with a combination of ConA and PMA and compared with the cytokine profiles of pre-established atopen-specific Th1 (AA42) and Th2 (AA60) clones.

mediated by contact allergen-specific $CD8^+$ T cells [2]. It should be considered, therefore, that the difference between patients and non-allergic control individuals may lie in the frequency and function of T cells from this subset. Other protocols are required to investigate this possibility.

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